The Influence of Intravascular Volume Expansion on Cerebral Blood Flow and Blood Volume in Normal Rats

Michael M. Todd, M.D.,* Julie B. Weeks, B.S.,† David S. Warner, M.D.‡

Background: Intravascular volume expansion can increase cerebral blood flow (CBF) in patients with cerebral ischemia. However, the changes in CBF produced by volume expansion in the normal brain remain the subject of debate, and the changes on cerebral blood volume (CBV; one determinant of intracranial pressure) have not been described. The effects of acute nondilutional volume expansion on cardiac output (CO), CBF, and CBV in normal rats were examined.

Methods: Normocarbic, normothermic halothane/N₂O-anesthetized rats were given 0, 6, 12, 24, or 36 ml of a blood–hetastarch mixture (n = 6 for each group). When volume loading was completed, H₃⁻nicotine was used to measure CBF, while ⁹⁹ᵐTe-labeled red cells and ¹⁴C-dextran were used to measure cerebral red cell and plasma volumes. Animals were killed by microwave irradiation (8KW × 770 msec). In different animals, cardiac output (CO) was measured by thermodilution during the infusion of 36 ml of blood–hetastarch.

Results: Central venous pressure (CVP) increased from 3.9 ± 0.7 mmHg (mean ± SD) in control animals to 13.0 ± 2.0 mmHg in rats given 36 ml of blood. Cardiac output increased to 138 ± 11% of control. There were no changes in arterial Hct or mean arterial pressure. There were no significant changes in CBF (which varied from 127 ± 22 ml·100 g⁻¹·min⁻¹ in controls to 102 ± 14 after the infusion of 36 ml). However, CBV increased in a linear fashion with increasing CVP, from 2.96 ± 0.57 ml/100 g in control conditions to 4.47 ± 0.83 ml/100 g after the infusion of 36 ml of blood/hetastarch.

Conclusions: In normal brain, CBF does not change during volume expansion, in spite of an increase in CO. This contradicts earlier studies, the results of which indicate an independent role for cardiac output in CBF control. Cerebral blood volume increased in proportion to CVP, suggesting simple passive venous distention. Whether this could increase ICP and compromise cerebral perfusion remains unclear. (Key words: Brain: cerebral blood flow; cerebral blood volume. Fluids, hetastarch. Heart: cardiac output. Hypervolemia. Measurement techniques: indicator fractionation; microwave irradiation.)

INTRAVASCULAR volume expansion (hypervolemia) has been used for the treatment of cerebral ischemia, particularly that caused by vasospasm following subarachnoid hemorrhage.¹,² However, while such therapy can increase cerebral blood flow (CBF),³,⁴ the cause of this change remains unclear, because volume expansion can alter blood pressure, hematocrit, and cardiac output. Although both hypertension⁵–⁸ and reductions in hematocrit⁷,⁹,¹⁰ can increase CBF in some situations, the independent influence of cardiac output on CBF in the normal and the ischemic brain remains controversial. Several workers have suggested that cardiac output may play some role,¹¹–¹³ although other studies fail to show any direct relationship.¹⁴,¹⁵ In addition, volume expansion may influence cerebral hemodynamics by increasing intracranial pressure, because of increased cerebral blood volume (CBV) resulting from increased venous pressure.¹⁶,¹⁷

In view of these uncertainties, the current study was designed to examine the influence of increasing intravascular volume (and central venous pressure) on CBF in rats. Volume expansion was carried out in a fashion that minimized alterations in either hematocrit or arterial blood pressure, although cardiac output (measured by thermodilution in a separate group of animals) was allowed to increase. In addition, CBV was also measured in an effort to determine its relationship to changing systemic venous pressure.

Materials and Methods

All experiments were approved by the University of Iowa Animal Care and Use Committee. Male Sprague-Dawley rats weighing 385 ± 22 g (mean ± SD) were placed in a plastic box and initially anesthetized with
4% halothane in O₂. When rats became unresponsive, a tracheostomy was performed after infiltration of neck tissues with 1% lidocaine. The animal’s lungs were mechanically ventilated to achieve normocarbia, using a tidal volume of ≈3.5 ml and rate of ≈55 breaths/min, with an inspired halothane concentration of 1%, and an FIO₂ of 0.4 (balance N₂). Rectal temperature was maintained at approximately 38°C.

With the animal supine, both groin areas were infiltrated with 1% lidocaine, and bilateral femoral arterial and venous catheters (PE-50) were placed surgically. One of the venous catheters was connected to a transducer and advanced cephalad until its tip rested within the intrathoracic vena cava or right atrium, as evidenced by the appearance of a typical central venous pressure tracing (which fluctuated with both the cardiac cycle and positive pressure ventilation). Venous and arterial pressures were monitored continuously thereafter. The remaining catheters were used for drug, isotope, and fluid/blood infusion or withdrawal.

When surgery was complete (which required ≈55 min), the animals were turned prone, placed in a Plexiglas cylinder with a preformed cone for the animal’s head/neck at one end, and positioned with the head in the waveguide of a microwave fixation unit (Cober Vivostat; Cober Electronics, Stamford, CT). Blood (0.4 ml) was withdrawn for initial blood gas and hematocrit measurements. Inspired halothane concentration was then reduced to 0.6%, and supplemented with 60% N₂O, balance O₂. Ten minutes later, a stop-watch was started, and the animals were assigned to one of five experimental groups, depending on the planned degree of volume expansion (n = 6 each). In group 1, no further interventions were undertaken (controls). Group 2 animals were given 6 ml of a mixture of heparinized whole rat blood mixed with 6% hetastarch (final mixture Hct = 31%).§ Animals in group 3 were given 12 ml of blood/hetastarch (final mixture Hct = 26%). Animals in group 4 received 24 ml of blood/hetastarch (final mixture Hct = 21%), while those in group 5 were given 36 ml (mixture Hct also = 21%). In all groups, blood was infused at the rate of ≈1 ml/min. To insure that volume expansion was completed at the same time in all animals (i.e., 36 min later), the start of volume loading in groups 2–5 was delayed for ≈29, 24, 11, and 0 min, respectively. One minute after completion of the volume load (i.e., at t = 37 min after starting the clock), 0.4 ml of blood was taken for final blood gas and hematocrit determination.

Thirty-eight minutes after starting the clock (and ≈2 min after completion of volume loading), 0.2–0.3 ml of rat red blood cells labeled with ≈30 μCi of ⁹⁹mTc and mixed with 12 μCi of ¹⁴C-dextran (70,000 molecular weight; New England Nuclear, Boston, MA) in 120 μl saline were given. Red cells were labeled with sodium pertechnetate obtained from the UI Nuclear Pharmacy, using a Cadema Medical Products kit (Middleton, NY). Four minutes and 15 s later, 50 μCi of ⁴¹H nicotine (New England Nuclear) diluted in 0.7 ml of normal saline was infused into the right femoral vein at a fixed rate of 0.726 ml/min. Blood was simultaneously withdrawn at the same rate from the left arterial catheter into a preweighed syringe. After 40 s of infusion/withdrawal, a timer shut the pump off and both infusion and withdrawal catheters were clamped to ensure no further movement of isotope into or out of the animal. The brain was immediately fixed in situ by microwave irradiation (≈8 kilowatts of incident power for 770 msec). Blood (2 ml) was drawn from the right arterial catheter to permit the determination of arterial hematocrit and the activity of both ⁹⁹mTc and ¹⁴C.

Sample Processing

Brain. The brain was removed from the skull as quickly as possible, the sagittal sinus and any adherent dura were removed, and the forebrain and hindbrain separated at the level of the colliculi. The forebrain was then divided into left and right hemispheres. These pieces were then transferred into individual 15 × 85-mm test tubes and weighed. (Note: the cerebral hemispheres were actually cut into anterior and posterior portions to facilitate processing. The values for these two portions were combined into a single hemispheric value for final analysis.) ⁹⁹mTc radioactivity in each tube was determined using a well counter (see below). The tissue samples were then transferred into scintillation vials and mixed with 4 ml of TS-1® solubilizer (Research Products International, Mt. Prospect, IL). The vials were placed in an oven at 50°C for 24 h until the tissue was dissolved. The contents were neutralized with glacial acetic acid and suspended in 14 ml of

§ The infusion of undiluted whole blood resulted in progressive increases in Hct by the time CBF/CBV measurements were made. Because we hoped to examine the influence of volume expansion without any change in Hct, it was necessary to dilute the infused blood with hetastarch, and a greater degree of dilution was needed for animals given larger volumes. These dilution factors were determined in a series of pilot animals.
VOLUME EXPANSION, CBF, AND CBV

3a70\textsuperscript{®} scintillation cocktail (Research Products International).

**Blood.**\textsuperscript{99m}Tc activity was determined in 50-\textmu l samples of whole blood. Additional 50-\textmu l samples of separated plasma were placed in scintillation vials, mixed with solubilizer (TS-1\textsuperscript{®}), heated to 50\degree C, and, finally, neutralized with glacial acetic acid and suspended in 3a70\textsuperscript{®}.

The volume of blood in the withdrawal syringe and its attached PE-50 tubing was determined by weighing (after rinsing the tubing with heparinized saline and correcting for the specific gravity of the blood/heparin mixture). Fifty-milliliter samples of this saline–blood mixture were solubilized, decolorized with benzoyl peroxide, neutralized as above, and suspended in 3a70\textsuperscript{®}. After counting, the values were used to calculate the total \(^{3}H\) activity in the withdrawal syringe. In addition, 50-\textmu l samples of whole blood were also processed and counted in a similar manner.

**Sample Counting.** \textsuperscript{99m}Tc activity was determined in tissue and blood using a well counter (Abbott Laboratories Logic Model 111 Well Counter; North Chicago, IL). Counts from all samples were back-corrected to a fixed time in time, using a \textsuperscript{99m}Tc half-life of 6.1 h. All scintillation vials were stored in the dark for 1 week to allow for the decay of \textsuperscript{99m}Tc activity. \(^{14}C\) and \(^{3}H\) activities were then determined in a Searle Mark III Model 6880 counter (Tracer Analytic, Middleton, WI).

**Calculations**

Volumes were calculated according to the following equations.

The specific activity of red blood cells (RBC) was calculated as:

\[
\frac{\text{\textsuperscript{99m}Tc/\mu l}}{\text{RBC}} = \frac{\text{\textsuperscript{99m}Tc/50 \textmu l}}{\text{WB}} \times \frac{\text{50 \textmu l}}{\text{RBC/50 \textmu l}}
\]  

(1)

where WB = whole blood.

Cerebral red cell volume (CRCV) was calculated as:

\[
\text{CRCV} = \frac{\text{\textsuperscript{99m}Tc per g of brain}}{\text{\textsuperscript{99m}Tc per \mu l of RBC}}
\]  

(2)

Cerebral plasma volume (CPV) was calculated as:

\[
\text{CPV} = \frac{\text{\textsuperscript{14}C per g of brain}}{\text{\textsuperscript{14}C per \mu l of plasma}}
\]  

(3)

For both CRCV and CPV, the resultant values were converted to units of ml/100 g. Total cerebral blood volume (CBV, also ml/100 g) was calculated as the sum of CRCV and CPV, while cerebral tissue hematocrit was calculated as:

\[
Hct_{\text{tissue}} = \frac{\text{CRCV}}{\text{CRCV} + \text{CPV}}
\]  

(4)

Cerebral blood flow (in ml · 100 g \(^{-1}\) · min\(^{-1}\)) was calculated by the indicator fractionation method,\textsuperscript{18,19}

\[
\text{CBF} = \frac{(\text{Ref syringe flow} \times \text{Tissue}^{3}H \text{ dpm})}{\text{Ref syringe dpm's}}
\]  

(5)

Tissue weight

Reference syringe flow was 0.726 ml/min.

**Cardiac Output Determinations**

In a separate group of five identically anesthetized rats, the hemodynamic consequences of volume expansion were determined. Surgical preparation was similar to that above, except for the placement of a 0.029" diameter (\(\approx 24 \text{ G}\)) K-type thermocouple (Type PT-6; Physitemp Instruments Inc., Clifton, NJ; response time constant 0.01 s) into the aortic arch \textit{via} the left common carotid artery. This was connected to an Omega digital thermometer (Stamford, CT), and the output passed to a chart recorder. This system was used to record the changes in aortic blood temperature resulting from the injection of 0.4 ml of iced saline (0–4\degree C) into the central venous catheter. The total area under the washout curve was used to calculate the cardiac output by thermodilution.\textsuperscript{20,21} Note, however, that, because of the limitations described by Hayes \textit{et al.},\textsuperscript{21} no effort was made to calculate absolute output values. Instead, baseline cardiac output was defined as "100%," and subsequent measurements are expressed relative to this value. This can be done simply by dividing the average area under the baseline washout curves by the area under the subsequent curves.

Cardiac output was determined in triplicate in all rats under baseline conditions. The determinations were then repeated 5 min after completing the infusion of 12 ml of a blood–heparstarch mixture given at the rate of \(\approx 1\) ml/min. Mean arterial pressure, Hct, and arterial blood gases were also determined. Similar measurements were carried out after 2 additional 12-ml volume infusions (making a total of 36 ml).

**Data Analysis** Comparisons of MAP, CVP, Hct, \textit{P}_{a}\text{O}_{2}, \textit{P}_{a}\text{CO}_{2}, pH, and body temperature among the five volume groups were performed using a one-way factorial ANOVA with \textit{post hoc} Newman-Keul testing. Intergroup differences in CBF, CPV, CRCV, CBV, cerebral...
Hct, and blood/brain Hct ratio were also examined via one-way ANOVA. In addition, the relationships between these latter variables and CVP were also examined "across groups" using linear regression analysis. Because data expressed as "percentage of baseline" are not normally distributed, changes in cardiac output were examined by performing a one-way repeated-measure ANOVA on log-transformed percentage values.

Results

Our efforts to increase intravascular volume with minimal changes in other parameters were generally successful, as shown in Table 1. Central venous pressure increased in proportion to the amount of blood given, while no changes were seen in mean arterial pressure, PaO₂, or body temperature. There were significant but, probably, unimportant differences between the five groups in Hct, Pao₂, and pH.

Scattergrams with fitted regression lines and 95% confidence intervals for central venous pressure versus CBF, CPV, CRCV, CBV, cerebral Hct, and brain/blood Hct ratio are shown in Figures 1 and 2. There was no relationship between venous pressure and CBF, but significant positive relationships were noted between CVP and both CPV and CBV. As a result of the relative changes in plasma and red cell volumes, cerebral Hct decreased as venous pressure increased. However, there was no significant change in the ratio of cerebral to arterial Hct, indicating that the changes in cerebral Hct were, at least in part, caused by changes in arterial Hct.

Changes in cardiac output during volume infusion are shown in Figure 3. As expected, output increased progressively during volume loading, reaching 138 ± 11% of baseline after the infusion of 36 ml of blood/hesastarch. Changes in MAP, arterial blood gases, Hct, etc., are similar to those noted above. In three of the five animals, CVP was not measured and, therefore, it was not possible to examine the relationship between CVP and CO.

Discussion

Our results indicate that normotensive, nondilutional volume expansion did not influence CBF, but did increase CBV in normal animals. This study was prompted by several controversies that exist in the medical literature. As mentioned, volume expansion, often com-

<table>
<thead>
<tr>
<th>Table 1. Consequences of Volume Expansion</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Volume infused (ml)</td>
</tr>
<tr>
<td>Group 1</td>
</tr>
<tr>
<td>0</td>
</tr>
<tr>
<td>MAP* (mmHg)</td>
</tr>
<tr>
<td>CVP* (mmHg)</td>
</tr>
<tr>
<td>Hct* (%)</td>
</tr>
<tr>
<td>Pao₂† (mmHg)</td>
</tr>
<tr>
<td>Paco₂† (mmHg)</td>
</tr>
<tr>
<td>pH† (units)</td>
</tr>
<tr>
<td>Rectal temperature* (°C)</td>
</tr>
<tr>
<td>CBF† (ml·100 g⁻¹·min⁻¹)</td>
</tr>
<tr>
<td>CPVF (ml·100 g⁻¹)</td>
</tr>
<tr>
<td>CRCVF (ml·100 g⁻¹)</td>
</tr>
<tr>
<td>CBVF (ml·100 g⁻¹)</td>
</tr>
<tr>
<td>Cerebral Hct (%)</td>
</tr>
<tr>
<td>Brain/blood Hct ratio†</td>
</tr>
</tbody>
</table>

Values are mean ± SD.

MAP = mean arterial pressure; CVP = central venous pressure; Hct = hematocrit; CBF = cerebral blood flow; CPV = cerebral plasma volume; CRCV = cerebral red cell volume; CBV = cerebral blood volume.

* Values were determined immediately before the measurement of CBF/CBV.

† The results of a one-way factorial ANOVA comparing the five experimental groups.

‡ The ANOVA results for a regression analysis of the appropriate variable versus measured CVP (all groups combined).

§ Significantly different from group 1.

†† Scattergrams, fitted regression lines, and confidence intervals for the last five variables can be found in Figures 1 and 2.

Anesthesiology, V 78, No 5, May 1993
VOLUME EXPANSION, CBF, AND CBV

Fig. 1. Scattergrams with fitted regression lines and 95% confidence intervals for the three directly measured cerebrovascular parameters (CBF = cerebral blood flow, CRV = cerebral red cell volume, and CPV = cerebral plasma volume) versus central venous pressures (CVP). Each point represents information from one animal. Regression equations, r values, and significance are included with each graph.

Fig. 2. Scattergrams with fitted regression lines and 95% confidence intervals for the three calculated parameters (cerebral blood volume (CBV), cerebral tissue Hct, and brain/blood Hct ratio) versus central venous pressures (CVP). Each point represents one animal. Regression equations, r values, and significance are included with each graph.

Combined with hemodilution, is used to treat patients with focal ischemic deficits of recent onset. The results have been mixed, with some studies showing clinical improvement\(^1,2,22,23\) and others demonstrating no benefit.\(^24-26\) This seems to be at variance with a large body of animal literature examining the influence of volume expansion in which increases in CBF and/or reductions in infarct volumes have been shown.\(^7,10,27-29\) Unfortunately, the mechanisms by which volume expansion can exert its effects remain unclear, and may be caused by changes in blood pressure, cardiac output, or hematocrit.
A variety of methodologic issues need to be discussed before considering our results. These experiments employed a unique triple-label method to allow simultaneous determination of CBF and CBV. This exploits the short half-life of the gamma-emitting isotope $^{99m}$Tc ($t_{1/2} = 6.1$ h), which is used to label red blood cells. Immediately after the animal is killed, the cerebral red cell distribution space (CRV) is determined by counting $^{99m}$Tc in both brain and blood in a simple well counter. This counter is "blind" to the presence of both $^3$H and $^{14}$C. Immediately after this is completed, the blood and brain samples are solubilized and then allowed to sit for 5 days to allow for the complete decay of the $^{99m}$Tc, at which time the remaining $^3$H and $^{14}$C activity (used to determine CBF and the cerebral plasma distribution space) can be determined by standard double label scintillation counting.

We have also employed microwave fixation to prevent the loss of intravascular radioactive tracers during removal of the brain. This technique evolved as part of our efforts to simultaneously measure CBF and CBV in rats. Measurements of CBF using such tracers as nicotine or iodoantipyrine require a well defined "stop flow" time. Because most of the tracer is located in tissue, little loss occurs during removal of the brain. However, the measurement of CBV with nondiffusible, intravascular tracers poses another set of problems, because the tracer can clearly leave the intravascular space if the brain is removed in an unfixed state (as blood leaks from the cut blood vessels). This can be prevented by freezing the brain in situ (e.g., by covering the skull with liquid nitrogen). However, because liquid N$_2$ requires 30–45 s to freeze the intracranial contents, it is not possible to accurately determine CBF (because of the lack of a precise stop flow time). Microwave fixation solves both of these problems simultaneously, by heat fixing the intracranial contents within less than 1 s. Tracer inflow is immediately stopped, and coagulated blood cannot leave the intracranial space.

We also made an effort to determine the relative changes in cardiac output produced by volume expansion. This method has been used in rats by others. We did not precisely quantitate output, because this would have required information we did not have and assumptions with which we were uncomfortable. For example, the calculation of absolute cardiac output requires knowledge of the amount of "cold" lost between the injection site and the recording thermister. Hayes et al. have shown in the rat that major inaccuracies can be encountered in attempting such calculations, but also noted that the method was reasonable for comparing repeated measurements within a single animal. Therefore, we chose only to estimate the change in output produced by volume expansion, relative to the baseline condition, and assumed that all factors leading to the gain of heat or loss of indicator remained constant. The magnitude of the changes observed are similar to those seen with volume expansion both in the rat and in humans.

Finally, we used a blood–hetastarch mixture for volume expansion. In initial pilot experiments, we administered only whole blood. However, this led to progressively increasing hematocrits. We believe that this is caused by different effective volumes of distribution for administered red cells and plasma, with a portion of the administered plasma leaving the intravascular space. To prevent this change in arterial hematocrit, it was necessary to administer an "excess" amount of plasma (or plasma substitute), and, thus, we used a diluted mixture of blood and hetastarch. Hetastarch was chosen for practical reasons. First, it was more readily available (and less expensive) than rat plasma. More importantly, however, we have already used hetastarch as a volume expander and hemodiluant in several rat studies, and have data on the CBF and CBV consequences of these interventions. It should, of course, be noted that, with this approach, the injection of 36 ml of blood/hetastarch results in a total increase in intravascular volume that is less than 36 ml. An effort was made to directly quantitate this change in several rats. Normal circulating blood volume in rats

---

Anesthesiology, V 78, No 5, May 1993
prepared as mentioned above (measured as the distribution space of $^{99m}$Tc-labeled RBC) is ≈21 ml (5.2% of body weight). In two additional rats, blood volume was again measured after the infusion of 36 ml of blood/hetastarch, with resultant values of 34–38 ml, an increase of 13–17 ml. A similar value (17 ml) is obtained by simply calculating the fraction of plasma/hetastarch that must be retained in the intravascular space after the injection of 36 ml of a mixture having a Hct of 21%, again assuming that the final intravascular Hct does not change and that no administered red cells are lost.

Our findings demonstrate that, in normal rats, volume expansion without hemodilution does not alter CBF, although cardiac output increased substantially. There are several implications of this. First, it supports the belief that cardiac output per se probably has little influence on normal CBF.15-19 This does not rule out the possibility that cardiac output may play a role in controlling CBF in ischemic tissue,13 but it also supports the belief that any beneficial effects of volume expansion on CBF are probably caused by the concomitant reduction in hematocrit and/or to increases in arterial perfusion pressure.

Volume expansion is also accompanied by increases in venous pressures, and a few comments need to be made regarding our observed changes in CBV. It has long been known that ICP varies directly with changes in venous pressure.16,17 Because these ICP changes are rapid, they must represent fluctuations in blood volume. However, only Brazy has made any effort to directly examine the CBV effects of changing venous pressure.30 He carried out a series of studies using transcranial near-infrared spectroscopy in neonates, and noted that intracranial blood volume rose during crying. Because much of the increase was caused by an increase in the amount of desaturated blood, he argued that the cause was related to increases in venous pressure and distention of postcapillary structures. Our methods do not allow us to define the anatomical location of the observed changes in CBV. However, the linear relationship between CVP and CBV occurring in the absence of any change in arterial perfusion pressure indicates that the increase is due to passive distention of compliant (venous?) structures. The magnitude of the CBV changes is striking. In a previous study, we examined the changes in CBV produced by alterations in $\text{Paco}_2$.37 We noted that an increase in $\text{Paco}_2$ of 20 mmHg increased CBV by 0.3 ml/100 g. Our current data indicates that a 3–7-mmHg increase in CVP can lead to a similar increase in CBV. It thus appears that clinically achievable changes in venous pressure caused by volume expansion (or perhaps by increasing intrathoracic pressure) can increase intracranial volume to a degree equivalent to that seen with rather large changes in $\text{Paco}_2$. We do not know the ICP consequences of these volume changes, although we would predict them to be small in these normally compliant animals. We also do not know what the slope of the CVP/CBV curve would be in the presence of preexisting intracranial hypertension. However, these findings do reinforce the belief of many clinicians that adequate ICP control is as dependent on maintaining a low venous pressure control (e.g., by maintaining adequate cerebral venous drainage) as it is on controlling $\text{Paco}_2$.

One final comment concerns the changing brain tissue hematocrit seen with volume expansion. Large vessel hematocrit is invariably higher than that seen in tissue. The typical ratio between brain and blood Hct is between 0.7 and 0.8. This is a manifestation of the so-called "Fähreus-Lindqvist effect."38,39 As blood moves through smaller and smaller tubes (and, thus, moves faster and faster), red cells move to the axial center of flow, leaving a jacket of plasma along the walls. Because the velocity profile across the vessel is conical (because of the greater resistance to flow at the plasma–endothelial interface), fluid at the center (red cells) moves much faster than that adjacent to the vessel walls (plasma). As a result, the transit time for red cells is less than for plasma. To conserve mass in the face of these differing transit times, there must be an "excess" of plasma in the tissue at any given moment, and, thus, tissue Hct must be less than that in large vessels.

This difference between arterial and tissue hematocrits can cause some difficulties in the determination of CBV. If only a single red cell or plasma marker is used, it is necessary to assume some constant ratio between arterial and tissue Hct. Under normal conditions, this is a reasonable assumption. However, several studies indicate that this ratio in not necessarily constant.30,40 For example, during hemodilution, we observed that the ratio of tissue to arterial Hct actually decreased progressively with falling arterial Hct, from a value of 0.78 at an arterial Hct of 42%, to 0.50 at an arterial Hct of 20%.30 No such change in Hct was seen during changing $\text{Paco}_2$,37 and only an insignificant change was seen in the current trial. Given this vari-
ability, we believe multitracer techniques may be preferable for the study of CBV, at least when large changes in either CBF, CBV, or plasma composition are expected.

In summary, our results indicate that volume expansion (and the accompanying increase in cardiac output) has little or no influence on CBF in normal brain, in rats anesthetized with halothane, but does lead to an increase in CBV. In addition, the rather steep slope of the CVP/CBV response curve indicates that changes in venous pressure may be more important in the determination of CBV (and, thus, ICP) than is generally believed.

References


31. Patlak CS, Blasberg RG, Fenstermacher JD: An evaluation of
errors in the determination of blood flow by the indicator fractionation and tissue equilibration (Kety) methods. J Cereb Blood Flow Metab 4:47–60, 1984


